DETAILED ACTION

Applicant's Response of 26 March 20101 and Status of the Claims

Applicant's Response filed 26 March 2010 has been entered, amending claims 31 and 36. The amendments overcome the objection of record of claim 36, which is WITHDRAWN. The claim amendments clarify the intended subject matters of claims 31 and 36. Claims 27, 31, and 36 remain in the application and are examined herein.

Double Patenting: Non-Statutory

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. **A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s)**. See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 27 remains rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of **US 5,585,258**. Applicant's arguments at pages 3 and 4 of the Remarks filed 26 March 2010 have been fully considered but are not persuasive. Applicant traverses the rejection of record as having been improperly based on teachings of the patent specification rather than the description of the patented claim itself, asserting that only the patent claims, and not the teachings of the patent specification, can be the proper basis for stating a rejection for obviousness-type double patenting. It is agreed that statements in the rejection of record to which Applicant points were unnecessary. The patented claim 1 states:

> 1. A composition **comprising a Hepatitis C Virus NS3 domain protease** or an active Hepatitis C Virus NS3 domain protease truncation analog. (emphasis supplied)

Claim 27 herein states:

27. A composition comprising a purified polypeptide comprising the amino acid sequence of SEQ ID NO:70.

Applicant does not dispute that the patented claim 1 is drawn to a composition of matter, which may be a polypeptide, comprising at least the amino acid sequence of a Hepatitis C Virus NS3 domain. Nor does Applicant dispute that the pending claim 27 is drawn to a composition of matter, which is a purified polypeptide, that comprises the 686-amino acid sequence of SEQ ID NO:70 which constitutes a Hepatitis C Virus NS3 domain. While the scope of the patented claim 1 may be broader than that of pending claim 27, a composition of the pending claim 27 is clearly also a composition of the patented claim 1. Double patenting results when the right to exclude granted by a first patent is unjustly extended by the grant of a later issued patent or patents. *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982). The rejection of record with respect to claim 27 is maintained until and unless an effective terminal disclaimer is filed.

Claim 31 remains rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 5 of **US 5,585,258** in view of Benson et al. **US 5,258,496**. Applicant's arguments at page 4 of the Remarks filed 26 March 2010 have been fully considered but are not persuasive. Applicant traverses the rejection of record as having been improperly based on teachings of the patent specification rather than the description of the patented claim itself, even when combined with the teaching of Benson et al. that recombinantly-produced fusion polypeptides are comprised in compositions during purification from a host cell wherein they are expressed. It is agreed that statements in the rejection of record to which Applicant points were unnecessary. The patented claim 5 states:

5. A fusion protein **comprising a fusion partner fused to a Hepatitis C Virus NS3 domain protease** or an active Hepatitis C Virus NS3 domain protease truncation analog. (emphasis supplied).

Claim 31 herein states:

31. A composition comprising a recombinantly expressed polypeptide comprising the amino acid sequence of SEQ ID NO:86.

Applicant does not dispute that the patented claim 1 is drawn to a composition of matter, which is a fusion polypeptide, comprising the amino acid sequence of a fusion partner fused to a Hepatitis C Virus NS3 domain. Nor does Applicant dispute that the pending claim 31 is drawn to a composition of matter comprising the 841-amino acid sequence – a polypeptide – of SEQ ID NO:86 wherein an amino acid sequence region of a human superoxide dismutase fusion partner is fused to the amino acid sequence of a Hepatitis C Virus NS3 domain. While the scope of the patented claim 5 may be broader than that of pending claim 31, a composition of

the pending claim 31 is clearly also a composition of the patented claim 5. Double patenting results when the right to exclude granted by a first patent is unjustly extended by the grant of a later issued patent or patents. *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982). The rejection of record with respect to claim 27 is maintained until and unless an effective terminal disclaimer is filed.

Claim 36 remains rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of **US 5,597,691**. Applicant's arguments at page 5 of the Remarks filed 26 March 2010 have been fully considered but are not persuasive. Applicant again traverses the rejection of record as having been improperly based on teachings of the patent specification rather than the description of the patented claim itself. It is agreed that statements in the rejection of record to which Applicant points were unnecessary. The patented claim 1 states:

> 1. A method for assaying compounds for activity against hepatitis C virus comprising the steps of:
>
> providing an NS3 domain hepatitis C virus protease or active NS3 domain hepatitis C virus protease truncation analog and a NS3 domain hepatitis C virus protease peptide substrate;
>
> contacting said protease or protease truncation analog with a candidate inhibitory compound in the presence of said peptide substrate; and
>
> measuring the inhibition of the proteolytic activity of said NS3 domain hepatitis C virus protease or protease truncation analog.

Claim 36 herein states:

> 36. A method for assaying compounds for activity in the presence of the composition of claim 31 comprising the steps of
>
> a) providing a solution containing the composition of claim 31;
>
> b) contacting said solution with a candidate inhibitory compound, and
>
> c) measuring the inhibition of the proteolysis of said purified polypeptide.

The patented claim 1 is thus drawn to an assay that requires that a polypeptide, which may be a fusion polypeptide, comprising the amino acid sequence of a Hepatitis C Virus NS3 domain be used to measure the inhibition of proteolytic activity associated with the polypeptide when contacted with a candidate inhibitory compound. The patented claim 1 explicitly requires the presence of a peptide substrate and one of ordinary skill in the art would understood that the patented claim 1 inherently requires that the polypeptide, candidate inhibitor, and substrate all be present in a solution in order that proteolytic activity occur and that proteolytic activity be

inhibited upon contact between a candidate inhibitor and a protease. The pending claim 36 is also drawn to an assay for measuring the inhibition of proteolytic activity, i.e., "proteolysis", requiring the presence of the fusion polypeptide of claim 31 when contacted with a candidate inhibitory compound. The pending claim 36 explicitly requires that the components of the assay be present in solution and also requires, albeit obliquely, that a substrate – "said purified polypeptide" – also be present. While the scope of the patented claim 1 may be broader than that of pending claim 36, an assay of the pending claim 36 has all of the components that are required for the assay of the patented claim, and *vice versa*, and both the patented claim 1 and the pending claim 36 measure the inhibition of proteolysis of a composition of matter, a peptide or polypeptide, having peptide bonds. There is nothing in the patented claim 1 or the pending claim 36 permitting any particular distinction between the substrates utilized in the claimed assays. Double patenting results when the right to exclude granted by a first patent is unjustly extended by the grant of a later issued patent or patents. *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982). The rejection of record with respect to claim 27 is maintained until and unless an effective terminal disclaimer is filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 36 remains rejected for reasons of record under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant's arguments at pages 5 and 6 of the Response filed 26 March 2010 have been fully considered but they are not persuasive to overcome the rejection of record of claim 36. Applicant believes that the claim amendment renders the rejection of record moot by omitting any explicit use of the term "substrate" with which an assay might be conducted while also requiring that the components of the assay be present in a "solution", asserting that the "amended[ ] claim 36 closely mirrors the Example 5." Yet the amended claim 36 actually does require the proteolysis of a particular molecule – "said purified polypeptide" – thus essentially requires that the inhibition of proteolysis of a substrate be measured. As noted in the rejection of record in the communication mailed 5 October 2010, the disclosure must establish Applicant's possession, at the time the application was originally filed, of an assay that can,

indeed, detect inhibitors of an HCV NS3 domain protease, here as a fusion partner with another protein in solution, in the presence of a candidate inhibitor and a functional assay for detecting inhibitors of proteolysis using the fusion protein of SEQ ID NO:86, conducted in a solution comprising a candidate inhibitory compound, must also provide a substrate of the protease in that solution in order to produce measurable results, i.e., measurement of the cleavage of the substrate to determine whether or not it decreases, where a decrease in proteolytic activity permits detection of an inhibitor. The specification's Examples 4 and 5 provide the "P600" fusion polypeptide with the amino acid sequence set forth in SEQ ID NO:86 and Applicant had earlier asserted in the Response filed 15 May 2008 that this particular fusion protein comprising the entire NS3 domain may have an "NS2/NS3" proteolytic activity, allowing the fusion protein itself to function both as a protease and as its substrate. But the specification does not contemplate such an "NS2/NS3" proteolytic activity and the specification does not demonstrate that a NS2/NS3 cleavage, essentially an autocatalytic event, occurs. Instead, the NS2/NS3 autocatalytic metalloprotease activity takes place at a region of the HCV polyprotein absent from the NS3 domain of SEQ ID NO:70 within the P600 fusion protein of SEQ ID NO:86, and the carboxyl-proximal region of the NS2 domain where NS2/NS3 cleavage occurs was discovered after the filing date of the original disclosure of the present specification, thus could not reasonably be considered by the artisan to have been in Applicant's possession at the time the specification was originally filed. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano,* 25 USPQ2d 1601, 1605 (Fed. Cir. 1993).

Applicant had also asserted in the Response 15 May 2008 that an NS3 serine protease activity is disclosed in Examples 10 and 11 but the specification identifies no region within the HCV NS3 domain amino acid sequence constituting the carboxyl-proximal 80% of the amino acid sequence of SEQ ID NO:86 where proteolysis occurs, and does not discuss or suggest a serine protease activity of the integral NS3 domain. Instead, none of the HCV polyprotein regions that Sardana et al. report to be substrates that are cleaved by an HCV NS3 serine protease are disclosed or suggested in the specification and all of these regions are absent from the P600 protein of Examples 4 and 5. Applicant cited publications of Vishnuvardhan et al. and Barbato et al., made of record with Applicant's IDS in the Response filed 15 May 2008, but Applicant did not then, and does not now, suggest that the P600 fusion protein comprises any region of the HCV polyprotein that could serve as a self-substrate for P600 fusion polypeptide purportedly cleaved in Example 5. The cleavage sites Applicant had cited at pages 7 and 8 of

the15 May 2008-filed Response where an integral NS3 domain protease might act without assistance of the NS4A peptide that were subsequently identified by Lin et al., 1994, Bartenschlager et al., 1994, and Bartenschlager et al., 1995, all now of record herein, but none of these sites are present within SEQ ID NO:86. Where none are present, even in the P600 construct, the specification cannot be considered to have disclosed Applicant's possession of an HCV NS3 domain serine protease. Applicant had presented an ancillary argument at in the Response filed 15 May 2008 urging that the presence of human superoxide dismutase [hSOD] as an amino-proximal fusion partner reconstitutes a NS2/NS3 autocatalytic cleavage but this is unpersuasive because the mass of the cleavage fragment produced does not indicate that the cleavage was produced by HCV NS2/3 autocatalytic activity and such proteolytic activity, when it occurs in a naturally-occurring HCV polyprotein, is not a serine protease activity. The "test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the Inventor had possession at that time of the . . . claimed subject matter", *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983). The rejection of record is therefore maintained.

Claim 36 remains rejected for reasons of record 35 U.S.C. § 112, first paragraph, because the specification does not reasonably provide enablement for conducting an assay that might detect an inhibitor of the P600 fusion protein of SEQ ID NO:86 where there the specification teaches no substrate for a proteolytic activity that might be measured in order to detect inhibition of a proteolytic activity of a P600 fusion protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Applicant's arguments at page 6 of the Response filed 26 March 2010 have been fully considered but they are not persuasive. Applicant believes that the claim amendment renders the rejection of record moot by omitting any mention of a substrate with which an assay might successfully be conducted while having a "solution" mediate the contact between the protease-comprising composition and a candidate inhibitory compound. Applicant had previously suggested in the Response filed 15 May 2008, that the specification enables the preparation of a NS2/NS3 domain protease formed in the fusion with hSOD. The specification itself, however, teaches away from the preparation of anything other than a serine protease and provides no guidance that could help the artisan select the portion of the NS2 domain that must be included together with the NS3 domain amino acid sequence within the P600 fusion protein in order to conduct an autocatalysis. Indeed, the native NS2/NS3 autocatalytic of an HCV polyprotein was disclosed by others only after the application was filed. Applicant had also proposed at pages 19-21 of the Response filed 15 May 2008 that the specification discloses an adequate

substrate, "in the form of [the] HCV polyprotein" with which experimentation might be conducted, and that its use "for testing NS3 serine protease activity in trans", might require no undue experimentation on the part of the artisan to make HCV NS3 domain proteases commensurate in scope with the recitations of the claims rejected herein. With regard to what may constitute "undue experimentation", the CCPA, the precursor of the Court of Appeals for the Federal Circuit, determined that a **reasonable correlation** must exist between the **scope asserted** in the claimed subject matter and **the scope of the guidance** the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (emphasis supplied). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). Instead, the P600 fusion protein of SEQ ID NO:86 includes no amino acid sequence region that permits cleavage at the NS2/3 junction by a NS2/3 metalloprotease and includes none of the amino acid sequence regions, e.g., the NS3/4A, NS4A/4B or NS4B/5A junctions, where an Hepatitis C Virus NS3 domain serine protease cleaves. The specification provides no guidance that might direct the artisan to select the HCV NS5 domain as a substrate for serine protease activity. Indeed, the only substrates that the specification proposes, e.g., at pages 19-21 therein as discussed in the communication mailed 16 November 2007, are not the substrates of the NS3 domain serine protease within SEQ ID NO:86. Where the specification provides no guidance as to what more might be required for a claimed method beyond the particular P600 fusion protein having the amino acid sequence of SEQ ID NO:86, e.g., how to locate the sequence of NS4A cofactor, a region absent from SEQ ID NO:86, the specification fails to indicate the direction the artisan might take to begin the next, necessary, process of experimentation. The rejection of record is therefore maintained.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 36 is rejected under 35 U.S.C. § 112, second paragraph, because it recites the limitation "said purified polypeptide" in clause (c) of the claim. There is insufficient antecedent basis for this limitation in the claim preamble which requires a "composition of claim 31" and no basis for this limitation in the intervening clauses (a) and (b) of claim 36.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Andrew Wang, can be reached at 571.272.0811. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/William W. Moore/
Examiner, Art Unit 1656

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